REMARKS

Upon entry of this amendment, claims 1-3, 7-8, 10-14, 24 and 25-46 are pending. Claims 4-6 and 9 are hereby canceled.

The specification has been amended to correct clerical errors on pp. 11 and 12.

Claims 1-3, 7-8, 10-14 and 24 are amended. Claim 1 as amended requires that a substance P peptide be present "in a dose effective to inhibit growth of a bacterial cell". Support can be found in the specification, for example, on p. 3, line 3 and on lines 10-12, in Table 2, and in claim 24 as originally filed. Claims 2-3, 7-8, 10, 12 and 14 depend directly or indirectly from claim 1, so these claims are likewise amended.

Claim 11 as amended requires that a substance P peptide be present "in a dose effective to inhibit growth of a fungal cell". Support for this amendment is found in claim 11 as originally filed, and in the specification on p. 3, lines 8-9, and on p. 4, line 5. Claim 13 depends from claim 11 and is likewise amended.

New independent claim 31 relates to a composition comprising a fragment of a substance P peptide, wherein the fragment comprises antimicrobial activity and does not bind to a cell surface substance P peptide receptor. Support for claim 31 can be found in the specification on p. 12, lines 8-12.

Claim 24 is amended to be limited to substance P peptide as shown in SEQ ID Nos: 1 or 2, and further that the unit dose is effective to inhibit growth of a bacterial or a fungal cell, the claim also amended so that the kit also requires a physiologically acceptable carrier, a label and instructions for use. Support can be found on p. 10, lines 14-15, and p. 3, lines 3-4.

The claims as amended and the new claims are supported by the written description and the claims as originally filed. Support for new claim 25 can be found in claim 3 and claim 11 as filed; support for new claim 26 can be found claims 7 and 11 as filed; support for new claim 27 can be found in claims 10 and 11 as filed; support for new claim 28 can be found in original claims 11 and 14; support for new claims 29-31 can be found in the specification on p. 10, lines 14-16; support for new claim 32 can be found in the specification on p. 10, lines 16-17; and support for new claim 33 can be found in the specification on p. 10, lines 19-20. Support for new claims 34-37 can be found in the specification, for example, on p. 2, lines 25-27 and on p. 12 lines 24-28; support for new claims 40-43 can be found in the specification in Table 2 on p.

13, with the concentrations shown therein recalculated as molarity. Support for new claims 44-46 can be found in the specification for example on p. 2, lines 31-33.

No new matter has been added by this amendment. Applicants reserve the right to prosecute amended, cancelled, and withdrawn claims or claims having breadth and scope similar to those as originally filed in this or another application the having same priority date.

The claims are supported by the written description

The Examiner in Section 4 of the Office Action rejects claims 1-14 and 24 under 35 U.S.C. 112, first paragraph, stating that "...the specification broadly describes as a part of the invention polypeptides consisting of the polypeptides SEQ ID Nos: 1, 2, 12 and 13" and "...the specification provides insufficient written description to support the games encompassed by the claim."

Applicants have canceled claim 4, directed to a sequence that is at least 50% identical to the amino acid sequence of SEQ ID Nos. 1 or 2, and have canceled claims 5-6 and 9 directed to SEQ ID NO: 12 having 6 Xaa residues.

With respect to SP peptides in other claims, Applicants point out that a SEQUENCE IDENTIFICATION document was co-submitted with the application, both of which provide the exact and definite sequences of SEQ ID Nos. 1-11. The SEQUENCE IDENTIFICATION document also provides sequences which are listed in the specification on p. 11, line 21-p. 12, line 7 including Table 1. Table 2 of the specification is part of a working example that provides data on compositions including SEQ ID No: 1 (human SP), SEQ ID No: 2 (an SP antagonist), bradykin (SEQ ID No: 3), neurotensin (SEQ ID No: 4), and indolicidin (SEQ ID No: 5), as defined on p. 11. SEQ ID NO: 14 arose from a clerical error and no claims are remaining directed to this subject matter.

With respect to SEQ ID NO:13 (claim 8), Xaa at one terminus residue is defined as being any of the 19 naturally occurring amino acids other than methionine. Thus claim 8 encompasses only 19 possible sequences (i.e., a representative number of species), as discussed.

Applicants submit that the written description requirement has been met.

The claims are fully enabled

Claims 1-14 and 24 were rejected for overbreadth.

The Examiner rejects claims 1-14 and 24, stating, "...[t]here is no guidance provided as to which amino acids can be added, deleted or substituted and the polypeptide would retain its biological function."

In *In re Angstadt*, the court stated that "...appellants are not required to disclose every species encompassed by their claims even in an unpredictable art such as the present record presents, each case must be determined on its own facts." See 537 F. 2d 498, 503. The issue identified by that court is not that some experimentation is required, but whether the amount of experimentation is undue. The specification at p.5, line 26 to p. 6, line 6 provides details of how to test whether an SP spptide inhibits growth of a bacterial cell. Applicants submit that screening of a limited 19 compounds (i.e., the number of possible compounds encompassed by claim 8) to identify those which inhibit growth of a microbial cell, is not undue experimentation to one of ordinary skill in the art of microbiology. Moreover, determining a dose which inhibits a bacterial or fungal cell is also routine in the art of microbiology. As in *In re Angstadt*, 537 F. 2d 498, 190 U.S.P.Q. 214, Applicants here have added a functional limitation to the claims.

Claim 4 has been canceled. Claims 1-3, 7-8, and 10-14 have been amended to require a specific function, i.e., to inhibit growth of a bacterial or to inhibit growth of a fungal cell, thereby eliminating onoperable embodiments. Claim 24 has been amended to require a sequence as shown in SEQ ID Nos: 1 or 2, and a dose effective to inhibit growth of a bacterial or a fungal cell. The amended claims exclude inoperable embodiments. The specification provides two examples with detailed guidance regarding how to determine whether or not a composition falls within the scope of the claims. (See for example p. 13, lines 10-24.) Thus, the scope of the amended claims is commensurate with the disclosure provided in the specification. This rejection should therefore be withdrawn.

Applicants respectfully request that the Examiner withdraw rejection of claims under 35 U.S.C. § 112, first paragraph.

Claims as amended are novel over the prior art

The Examiner has rejected claims as anticipated under 35 U.S.C. 102(b) or 102(e) by each of the references listed below.

Claims 1, 11 and 24 are amended to require a dose effective to inhibit growth of a bacterial cell. Claims 2-4, 7-8, 10,12 and14 depend directly or indirectly on claims 1, and are therefore identically amended.

Claim 11 as amended is an independent claim directed to a composition comprising a substance P peptide in a dose effective to inhibit growth of a fungal cell. Claim 13 depends directly on claim 11, and is therefore identically amended. Claim 24 as amended is limited to SEQ ID NOs: 1 or 2, and includes a physiologically acceptable carrier, a label, and instructions for use.

As shown below, nothing in the prior art shows that a substance P peptide inhibits growth of a bacterial cell or a fungal cell, at any dose.

Folkers et al. (U.S. Patent No. 4,481,139, issued Nov. 6, 1984)

The Examiner alleges that Folkers et al. teaches compositions that comprise antagonists of substance P that are useful to elucidate some biological mechanisms of substance P and inflammatory responses in the eye for medical practice in ophthalmology, and thereby anticipates that present claims 1-11 under 35 U.S.C. § 102(b).

Folkers et al. shows only an agent which antagonizes the effects of SP on endogenous inflammatory responses in a guinea pig.

No methods or results are shown by Folkers et al. with a bacterial cell, a bacterial cell assay, nor a fungal cell, nor a fungal cell assay. Folkers fails to describe an anti-bacterial or anti-fungal effect of SP, at any dose, therefore this reference does not anticipate any of the claims as amended herein.

Applicants request withdrawal of rejection in view of Folkers et al.

Rosengurt et al. (WO 88/07551, published Oct. 6, 1988)

Claims 1-4, 7 and 10 are rejected under 35 U.S.C. § 102(b) as anticipated by Rosengurt et al., stating that Rosengurt et al. teach a composition comprising a substance P peptide. Claim 4 has been canceled so rejection of this claim is moot.

Further claims 1-3, 7 and 10 have been amended to require a dose of a substance P peptide effective to inhibit growth of either a bacterial or an a fungal cell. Rosengurt et al. fails to show or suggest any dose effective to inhibit growth of either a bacterial or an a fungal cell. Therefore, Rosengurt et al. does not anticipate the present invention as claimed in amended claims 1-3, 7 and 10.

Applicants respectfully request that the Examiner withdraw rejection of present claims 1-3, 7 and 10 in view of Rosengurt et al.

Horig J. (WO 83/01251, published April 14, 1983)

The Examiner rejects claims 1-10 under 35 U.S.C. § 102(b) as anticipated by Horig et al., stating that "Horig teaches a composition comprising peptides of the pharmaceutically acceptable salts and agents and/or conventional pharmaceutical adjuvants." Claims 4-6 and 9 are canceled, so rejection of these claims is moot.

No anti-bacterial activity was disclosed or suggested in this reference. No effective doses of a composition comprising a substance P in a dose effective to inhibit growth of a bacterial cell, as in present claims 1-3, 7-8 and 10, are shown by Horig.

Applicants in view of the present amendments and arguments request that the Examiner withdraw rejection of claims in view of Horig.

De Simone et al. (J. Clin. Lab Anal. 3:345-349, (1998))

The Examiner rejects claims 1-11 under 35 U.S.C. § 102(b) in view of De Simone et al., alleging that this reference teaches the effects of substance P on *Salmonella minnesota*. Claims 4- 6 and 9 have been canceled, so rejection of those claims is moot.

Present independent claims have been amended herein to require a dose of a substance P peptide effective to inhibit growth of a bacterial cell (claim 1) or a fungal cell (claim 11). De Simone et al. reports that SP inhibits binding of *Salmonella minnesota* to lymphocytes. This reference fails to describe or suggest a dose of a substance P peptide effective to inhibit growth of a bacterial cell or of a fungal cell. In fact, the bacteria in De Simone et al. were killed prior o any exposure to a substance P peptide.

Applicants request withdrawal of rejection of claims in view of De Simone et al.

Schroeder, C. (Acta virol., September 1986, 30(5) 432-35)

The Examiner rejects claims 1-11 under 35 U.S.C. § 102(b) as anticipated by Schroeder.

Schroeder shows that substance P inhibits measles virus replication in cell culture and partially blocks viral fusion activity, at an ID_{50} of 0.6 μmoles/l. See Schroeder, Abstract. In contrast to Schroeder, maximal inhibition of growth of bacterial cells as in the present claims is found with an effective dose, which as is shown in Table 2 on p. 13 of the specification is 0.003% indolicidin (or 14 μM, for *S. aureus*; see Declaration of Andrzej Lipkowski, attached, for calculation of molarity), 0.007% for indolicidin for *E. coli*, and 0.007% of SEQ ID NO:1 (44 μM)

for *S. aureus*. Further, inhibition of growth of fungal cells observed is with indolicidin an effective dose of a concentration of 0.015% (76 μM) and with 0.03% SEQ ID NO:2 (180 μM). These concentrations are at least two orders of magnitude greater than the concentration shown in Schroeder.

Therefore the effective dose of the present claims for inhibiting growth of a bacterial cell or a fungal cell is not the same as is disclosed in Schroeder, and further is not inherent in what is disclosed in Schroeder.

Applicants urge the Examiner to withdraw rejection of claims in view of Schroeder.

Visser et al. (WO 92/18536, published Oct. 29, 1992)

The Examiner rejects claims 1-7, 9 and 24 under 35 U.S.C.§ 102(b) as anticipated by Visser et al. Applicants have canceled claims 4-6 and 9, hence rejection of these claims is moot.

Visser et al. presents as the object of their invention "...to provide a method for detecting and localizing tissues having neurokinine 1 receptors in the body of a warm-blooded living being." Visser's pharmaceutical composition is "...labeled with a detectable isotope...". (p. 7, lines 5-6).

Further, Visser et al. shows no dose of any composition, let alone SP or its derivatives, effective to inhibit any bacterial cell as required by present claims 1-3, and 7, therefore Visser et al. fails to anticipate these claims. Visser's dose range as shown in Figures 1-4 is at its greatest concentration merely micromolar (10^3 nmolar). In contrast in the present invention, concentrations of the peptides shown in Table 2 on p. 13 of the specification are at least two orders of magnitude greater.

Claim 24 is directed to kit that lacks Visser's label with a detectable isotope, therefore present claim 24 is different from what is taught or suggested by Visser.

For these reasons, Visser et al. is not the same as the invention of the present claims, therefore Visser et al. does not anticipate the present claims. Applicants urge the Examiner to withdraw this rejection.

De La Charrier et al. (U.S. Patent Number 6,203,803, issued March 20, 2001)

The Examiner rejects claims 1-2, 7, and 11-14 under 35 U.S.C. 102(e) as anticipated by De La Charriere et al.

De La Charriere et al. concerns use of a SP antagonist to treat sensitive skin, and further to prevent and/or combat skin irritations, desquamation, erythemas, sensation of dyesthesia/overheating, or pruritis of skin.

No dose effective to inhibit growth of a bacterial cell nor of a fungal cell, as required by the present claims 1-2, 7, and 11-14, is shown by De La Charriere et al.

This reference does not anticipate the present claims. Applicants urge the Examiner to withdraw rejection of claims with respect to De La Charriere et al.

CONCLUSION

On the basis of the amendments and remarks, Applicants respectfully submit that the pending claims and specifications are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is invited and encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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MARKED-UP VERSION TO SHOW CHANGES MADE

In the claims:

1. (Amended) A [An antimicrobial] composition comprising a substance P peptide in a dose effective to inhibit growth of a bacterial cell.

2. (Amended) The [antimicrobial] composition of claim 1, wherein the amino acid sequence of the peptide comprises residues 1-8 of SEQ ID No: 1.

3. (Amended) The [antimicrobial] composition of claim 2, wherein the amino acid sequence of the peptide comprises residues 1-8 of SEQ ID No: 2.

7. (Amended) The [antimicrobial] composition of claim 1, wherein the amino acid sequence of the peptide comprises amino acids 1-10 of SEQ ID Nos: 1 or 2.

8. (Amended) The [antimicrobial] composition of claim 1, wherein the amino acid sequence of the peptide comprises Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Xaa (SEQ ID No: 13), wherein Xaa is not a methionine residue.

10. (Amended) The [antimicrobial] composition of claim 1, having at least one dextrorotatory amino acid.

11. (Amended) A [The antimicrobial] composition [of claim 1] comprising a substance P peptide in a dose effective to [,wherein the peptide inhibits] inhibit growth of a fungal cell [bacterium, fungus , or virus].

12. (Amended) The [antimicrobial] composition of claim [11] 1, wherein the [peptide inhibits growth of a] cell is selected from the genera consisting of *Staphylococcus*, *Streptococcus*, *Bacillus, Clostridium*, *Escherichia*, *Shigella*, *Campylobacter*, *Hemophilus*, *Proteus*, *Yersinia, Klebsiella, Pseudomonas*, and *Serratia*.

13. (Amended) The [antimicrobial] composition of claim 11, wherein the [peptide inhibits growth of a] cell is selected from the genera consisting of *Aspergillus*, *Candida*, *Cryptococcus*, *Epidermophyton*, *Histoplasma*, *Microsporum*, and *Trichophyton*.

14. (Amended) The [antimicrobial] composition of claim 1, further comprising a second [antimicrobial] antibacterial agent.

24. A kit comprising at least one unit dose of [an antimicrobial] substance P peptide [having at least 50% identity to positions 1-8 of] as shown in SEQ ID Nos: 1 or 2 in a physiologically acceptable carrier, wherein said dose is effective to inhibit growth of a bacterial or a fungal cell, the kit further comprising a label and instructions for use.

In the specification:

Please substitute the following paragraph for p. 3, lines 3-5.

Also within the invention is a kit containing at least one unit dose of an antimicrobial SP peptide or mimetic packaged together with a label, instructions for use, or means of administering the compound.

Please substitute the following paragraph for p. 11, lines 15-26.

Peptides were synthesized by respective Boc- or Fmoc- chemistry in solid phase by methods known in the art, e.g., Misicka, et al., Biochemical & Biophysical Research Communications 1991:180(3):1290-7. Crude peptides were purified by gel filtration on Sephadex LH-20 (in methanol), followed by preparative HPLC. All peptides were confirmed to have correct amino acid analyses and molecular weights by FAB-MS. For microbiological study, peptides in acetate form were used. The sequences of the peptides are: SP, Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-MetNH2 (Fig. 1, SEQ ID NO:1); SP antagonist, Arg-D-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-D-Trp-Leu-MetNH2 (SEQ ID NO:2); bradykinin, Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg (SEQ ID NO:3); neurotensin, Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu (SEQ ID NO:4)[or Xaa-Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu

(SEQ ID NO:14; where Xaa is Pyr or Tyr)]; and indolicidin, Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH2 (SEQ ID NO:5).

Please substitute the following paragraph for p. 11, lines 27-31.

SP is expressed in a variety of different animals (see Table 1 [Warren, L., http://www.wdv.com/Notebook/Biochemistry/Substance P/]). Analysis of the sequences of these homologues, in comparison to that of humans (SEQ ID No: 1) yields insight into design of SP peptides embodied herein. The sequence of SP native to the following organisms has been reported:

Please substitute the following paragraph for p. 12, line 21, to p.13, line 7.

Peptides having the above consensus offer advantages for use as a novel antimicrobial agent. As SP is an endogenous peptide, found in humans and other chordate and vertebrate animals, it is not antigenic. Therefore continued administration of this agent over time does not provoke an immune response. Further, deletion or substitution one or more of the three carboxy-terminal residues (Gly-Leu-Met) associated with affinity of the SP peptides to a specific SP receptor on cells of the immune system assures that possible undesired side affects of systemic SP administration (e.g., SP-receptor mediated activities such as pain, inflammation, and swelling) are reduced or eliminated. In addition, the antimicrobial activity of SP peptides has a broad antimicrobial spectrum as shown herein, including Gram positive and Gram negative bacteria, and fungi. These data indicate that traditional targets for antimicrobial agents, such as the prokaryotic ribosome or the murein cross-bridges of a bacterial cell wall are not involved as macromolecular targets. Therefore, the compounds described herein cannot be evaded by enzymes associated with multiple drug resistance factors. Topical administration of an SP peptide to an epithelium of a subject offers [teh] the advantage that the peptide remains external and does not become systemic.